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Infections, hospitalisations, and deaths averted via a nationwide vaccination campaign using the Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel: a retrospective surveillance study

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Summary

Background On Dec 20, 2020, Israel initiated a nationwide COVID-19 vaccination campaign for people aged 16 years and older and exclusively used the Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine (tozinameran). We provide estimates of the number of SARS-CoV-2 infections and COVID-19-related admissions to hospital (ie, hospitalisations) and deaths averted by the nationwide vaccination campaign.

Methods In this retrospective surveillance study, we used national surveillance data routinely collected by the Israeli Ministry of Health from the first 112 days (Dec 20, 2020, up to our data cutoff of April 10, 2021) of Israel's vaccination campaign to estimate the averted burden of four outcomes: SARS-CoV-2 infections and COVID-19-related hospitalisations, severe or critical hospitalisations, and deaths. As part of the campaign, all individuals aged 16 years and older were eligible for inoculation with the BNT162b2 vaccine in a two-dose schedule 21 days apart. We estimated the direct effects of the immunisation programme for all susceptible individuals (ie, with no previous evidence of laboratory-confirmed SARS-CoV-2 infection) who were at least partly vaccinated (at least one dose and at least 14 days of follow-up after the first dose). We estimated the number of SARS-CoV-2 infection-related outcomes averted on the basis of cumulative daily, age-specific rate differences, comparing rates among unvaccinated individuals with those of at least partly vaccinated individuals for each of the four outcomes and the (age-specific) size of the susceptible population and proportion that was at least partly vaccinated.

Findings We estimated that Israel's vaccination campaign averted 158 665 (95% CI 144 640–172 690) SARS-CoV-2 infections, 24 597 (18 942–30 252) hospitalisations, 17 432 (12 770–22 094) severe or critical hospitalisations, and 5532 (3085–7982) deaths. 16 213 (65·9%) of 24 597 hospitalisations and 5035 (91·0%) of 5532 of deaths averted were estimated to be among those aged 65 years and older. We estimated 116 000 (73·1%) SARS-CoV-2 infections, 19 467 (79·1%) COVID-19-related hospitalisations, and 4351 (79%) deaths averted were accounted for by the fully vaccinated population.

Interpretation Without the national vaccination campaign, Israel probably would have had triple the number of hospitalisations and deaths compared with what actually occurred during its largest wave of the pandemic to date, and the health-care system might have become overwhelmed. Indirect effects and long-term benefits of the programme, which could be substantial, were not included in these estimates and warrant future research.

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Introduction

The SARS-CoV-2 pandemic has already resulted in more than 220 million cases and 4·6 million deaths globally as of Sept 10, 2021.[1] Israel was one of the first countries to initiate a rapid, nationwide, COVID-19 vaccination campaign. The campaign, led by the Israel Ministry of Health, started on Dec 20, 2020, with the goal of administering the Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine (tozinameran) according to a schedule of two doses 21 days apart to all citizens aged 16 years and older.

Israel has a population of approximately 9·2 million people, of whom 6·5 million are aged 16 years or older. The BNT162b2 vaccine was offered to all residents of Israel, initially targeting health-care workers, long-term care-facility residents, people who are immunocompromised, and those aged 60 years and older. Vaccination was subsequently offered to younger age groups, and by Feb 4, 2021, all Israeli residents aged 16 years and older were eligible for vaccination.[2] By April 10, 2021, more than 10 million doses of the vaccine had been administered, with more than 70% of Israelis

Research in context

Evidence before this study

Since the start of Israel's nationwide vaccination campaign, we have been closely monitoring the scientific literature (PubMed and medRxiv) and press coverage to identify reports describing the effectiveness or the impact of the Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine (tozinameran) in a real-world setting. We searched PubMed and medRxiv for publications since database inception until Aug 3, 2021, with no language restrictions, using the terms "COVID-19", "vaccin*", "model", "effective*", "impact", "avert*", AND "reduc*". Observational studies from Israel and elsewhere describing the real-world effectiveness of BNT162b2 have been published. Additionally, preliminary evidence has emerged from Israel showing substantial decreases in SARS-CoV-2 activity corresponding with the rapid introduction of the vaccine. However, a paucity of data exist describing the estimated the number of SARS-CoV-2 infections and COVID-19-related admissions to hospital (ie, hospitalisations) and deaths averted by a nationwide vaccination campaign.

Added value of this study

We provide nationwide estimates of the number of COVID-19 cases, hospitalisations, and deaths averted via the direct effects of the vaccination campaign in Israel. We estimate Israel's COVID-19 vaccination campaign prevented thousands of hospitalisations and deaths.

Implications of all the available evidence

Our findings, in the context of other data showing high effectiveness of two doses of BNT162b2 against all SARS-CoV-2 outcomes and in all age groups, suggest that rapid introduction of vaccination and prioritising older populations is an effective strategy to prevent hospitalisations and deaths during surges of SARS-CoV-2 and to help control the pandemic.

aged 16 years and older having received two doses, including more than 90% two-dose coverage among adults aged 65 years and older.[3,4]

The vaccination programme started at the same time as a large wave of SARS-CoV-2 infections that resulted in a nationwide lockdown a week after the vaccination programme began, on Dec 27, 2020, with additional lockdown restrictions being implemented on Jan 8, 2021. Daily infections increased during this time, peaking at more than 10 000 on Jan 20, 2021. Phased easing of lockdown restrictions started on Feb 7, 2021, with the lifting of restrictions on local travel and the reopening of some workplaces, restaurants for take-away orders, and parks. On Feb 11, 2021, schools reopened for children in first through fourth grade (aged 6–9 years). Schools reopened for grades five, six, eleven, and twelve (children aged 10–11 years and 16–17 years) on Feb 21, 2021, and for grades seven through ten (children aged 12–15 years) on March 7, 2021, when the lockdown was lifted. Since the lifting of lockdown restrictions, rates of SARS-CoV-2 infections have generally remained low, with fewer than 150 new infections per day observed for the period April 23 to June 23, 2021; however, an increase in cases was observed starting on June 24, 2021, aligning with the introduction of the delta (B.1.617.2) variant of concern to the country.[3–5]

The setting of high vaccine uptake in Israel introduced during a time of high SARS-CoV-2 circulation has allowed for robust analyses of real-world vaccine effectiveness of BNT162b2 using national surveillance data and preliminary assessments of whether high vaccine uptake could control the pandemic.[4–6] Two analyses have found high effectiveness of BNT162b2 in Israel against all SARS-CoV-2 outcomes, including COVID-19-related admissions to hospital (ie, hospitalisations) and deaths, in all age groups, including older populations.[4,6] Reports have also indicated substantial decreases in the incidence of SARS-CoV-2 infections and COVID-19-related hospitalisations and deaths that corresponded with increasing vaccine coverage. These decreases were sustained even after the nationwide lockdown was lifted.[4,5] These findings corroborated data from the original randomised controlled trial of BNT162b2[7] and other preliminary reports of real-world effectiveness of BNT162b2 in other countries including Denmark,[8] the UK,[9,10] and the USA.[11]

However, the number of SARS-CoV-2 infections and COVID-19-related hospitalisations and deaths that have been averted via a nationwide vaccination campaign have yet to be estimated. Estimating the disease burden averted in a population after vaccine introduction would help to further elucidate and quantify the public-health benefits of vaccination, and such information is crucial for policy makers and the public. Israel, is a unique setting where early nationwide evaluation is possible, given its high population-level vaccine coverage and robust public health and technological infrastructure.[12] Here, we provide nationwide estimates of the burden of SARS-CoV-2 averted via the direct effects of Israel's vaccination campaign.

Methods

Study design and population

In this analysis, we estimated the number of SARS-CoV-2 infections and COVID-19-related hospitalisations, severe or critical hospitalisations, and deaths averted via the direct effects of Israel's nationwide vaccination programme, which started on Dec 20, 2020, until our data cutoff of April 10, 2021, among individuals aged 16 years and older. We included all individuals who had

received at least one dose of vaccine and had at least 14 days of follow up after their first dose. Hence, we began our analysis period 14 days after the start of the vaccination programme, on Jan 3, 2021.

In Israel, PCR testing for SARS-CoV-2 is widely available and provided with no out-of-pocket costs. PCR testing is required for people returning from travel abroad, close contacts of an infected person, or those with symptoms suggestive of COVID-19, such as fever or acute respiratory illness. However, anyone who wishes to be tested, regardless of symptoms, can do so without physician referral. Non-PCR-based testing was not used routinely in Israel during our study period. All cases identified via non-PCR-based testing are confirmed with PCR testing and only PCR-confirmed infections are counted as cases in national surveillance. All PCR-confirmed SARS-CoV-2 infections, hospitalisations, and deaths are reported to the Ministry of Health. In accordance with national guidelines, health-care providers attributed any hospitalisation or death among an individual with laboratory-confirmed SARS-CoV-2 infection to be due to COVID-19.[3,4] Surveillance data for SARS-CoV-2 infections and vaccine uptake are part of the national pandemic response and are collected under Public Health Ordinance 1940.[13] The Ministry of Health maintains a secure national database of people infected with SARS-CoV-2 and immunised with COVID-19 vaccine. The database contains personal identifiers for each record and is not open to the public. In this analysis, we only used country-wide daily-aggregate data that were de-identified before use.

Because data collection and analysis were done as part of Ministry of Health legal authority for public health surveillance under Public Health Ordinance 1940 and to support policy decision making and evaluation, no institutional review board review was required for this work.

Outcomes

We estimated the averted burden of four outcomes: SARS-CoV-2 infections and COVID-19-related hospitalisations, severe or critical hospitalisations, and deaths. As described previously,[4] SARS-CoV-2 infections were defined on the basis of laboratory-confirmed PCR positivity, and hospitalisations and deaths were attributed to COVID-19 according to national guidelines, which are based on international recommendations.[3,4] Hospitalisations were classified as severe if a patient had a resting respiratory rate of more than 30 breaths per min, oxygen saturation on room air of less than 94%, or ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of less than 300 mm Hg. Hospitalisations were defined as critical in the event of mechanical ventilation, shock, or cardiac, hepatic, or renal failure.[3,4,14]

Statistical analysis

On the basis of data from the original randomised controlled trial of BNT162b2[7] and consistent with real-world effectiveness studies,[4,6] we assumed that no vaccine protection was conferred fewer than 14 days after receiving the first dose. We calculated the number infections, hospitalisations, or deaths averted among all individuals who were at least partly vaccinated (defined as receipt of at least one dose and with at least 14 days of follow-up since the first dose) and two additional exposure group subsets of this population: fully vaccinated individuals (defined as those who received two doses, with at least 7 days of follow-up since the second dose, consistent with the definitions used in the previous randomised controlled trial of BNT162b2[7] and a nationwide analysis of real-world effectiveness of BNT162b2 in Israel based on the same data as we have been used in this analysis, albeit for a shorter time period[4]) and partly vaccinated individuals (defined as those who received only one dose, with at least 14 days of follow-up since the first dose, or two doses with fewer than 7 days of follow-up since the second dose).

We estimated the averted burden of SARS-CoV-2 outcomes in several steps. First, we excluded from the analysis people younger than 16 years and individuals with previous laboratory-confirmed SARS-CoV-2 infection (ie, these individuals were excluded from both the susceptible population and the counts of outcomes). Then, we calculated daily, age-specific (16–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years, with population sizes of each age stratum extrapolated from the 2021 census) incidence rates for people who were unvaccinated and for those who were at least partly vaccinated for each of our four outcomes. Person-days for the at least partly vaccinated and fully vaccinated groups were ascertained each day by multiplying the proportion of people who were in each vaccination category by the census estimates for each age stratum. Person-days for the unvaccinated group were determined each day by subtracting the number of person-days contributed by those who ever received BNT162b2 from the total census population for each age stratum. We then calculated, for each day in the analysis period, rate differences between these two groups with 95% CIs. Then, for each age stratum, we multiplied daily rate differences by the size of the susceptible population (ie, those with no previous evidence of laboratory-confirmed SARS-CoV-2 infection) and by the proportion who were at least partly vaccinated. This process was repeated for and summed across all days in the analysis period for each of the four outcomes to estimate the total burden of SARS-CoV-2 averted. The total burden of SARS-CoV-2 is summarised by

$$\sum_{\text{age stratum}=1}^{8} \sum_{\text{Jan 3, 2021}}^{\text{Apr 10, 2021}} N \times \text{Vx}_{\geq 1\text{ dose}} \left(\text{COVID}_{\text{UnVx}} - \text{COVID}_{\geq 1\text{ dose}}\right)$$

where N is daily total susceptible population size for each age stratum (ie, excluding those with previous

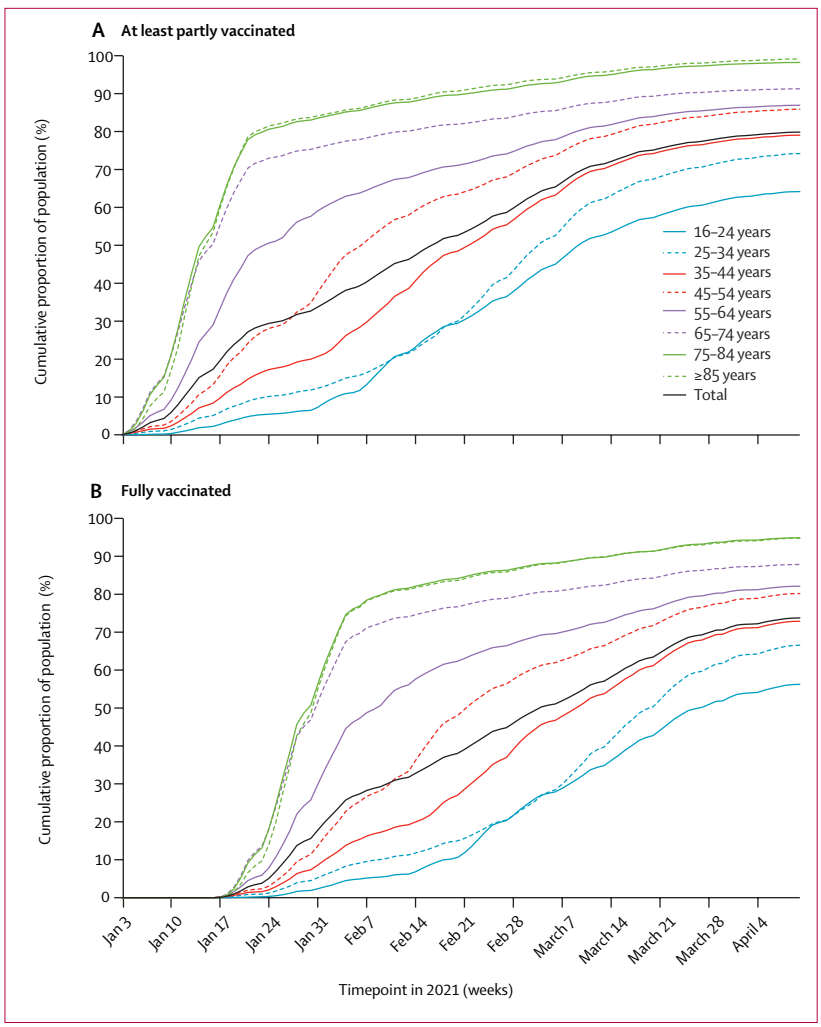

Figure 1: **Cumulative uptake of Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel by number of doses received and time since vaccination among people aged 16 years and older, Jan 3 to April 10, 2021**
Cumulative proportion of the population who were at least partly vaccinated (A) and who were full vaccinated (B). Dec 20, 2020, was the start of the Israel's nationwide vaccination campaign, but the analysis period started on Jan 3, 2021, which was the first day on which people could be at least partly vaccinated (defined as individuals who received at least one dose of BNT162b2 with at least 14 days of follow-up after the first dose). Fully vaccinated individuals are people who received two doses of vaccine with at least 7 days of follow up after the second dose. Week timepoints are indicted with the week starting on a Sunday.

evidence of laboratory-confirmed SARS-CoV-2 infection); $Vx_{\geq 1dose}$ is the daily cumulative proportion of people (within each age stratum) vaccinated with at least one dose of BNT162b2 with at least 14 days of follow-up after the first dose; $COVID_{UnVx}$ is the daily rate of SARS-CoV-2 infections and COVID-19-related hospitalisations, severe or critical hospitalisations, or deaths in the unvaccinated group; and $COVID_{\geq 1\ dose}$ is the daily rate of SARS-CoV-2 infections and COVID-19-related hospitalisations, severe or critical hospitalisations, or deaths among people who received at least one dose of BNT162b2 with at least 14 days of follow-up after the first dose (ie, at least partly vaccinated population). We used weighted averages of the variances for the rate differences in each age stratum to calculate SEs and corresponding 95% CIs for aggregated age groups (ie, age ≥16 years and ≥65 years).

Similar to our previous analysis,[4] when calculating incidence rates we determined person-days for vaccinated individuals for each day by multiplying the proportion of people who were at least partly vaccinated by population size estimates for each age stratum. We determined person-days for unvaccinated individuals for each day by subtracting the number of person-days contributed by those who were ever vaccinated from the total census population for each age stratum. Individuals with previous SARS-CoV-2 infection were excluded from person-day estimates. Finally, using the same methods, we determined the outcomes averted among those who were fully vaccinated and who were partly vaccinated. We estimated the number of outcomes averted among those who were partly vaccinated by subtracting the number of cases averted among the fully vaccinated population from the total number of cases averted among all those who were at least partly vaccinated.

We did all analyses using SAS (version 9.4).

Role of the funding source

The Israel Ministry of Health and Pfizer separately provided in-kind support to this study. No funds were exchanged as part of this collaboration. The funders of the study were involved in the study design, data analysis, data interpretation, writing of the report, and approved the decision to submit for publication. Only the Israel Ministry of Health was involved in data collection.

Results

By the end of the follow-up period (April 10, 2021), 5·2 million (79·8%) of 6·5 million Israelis aged 16 years or older were at least partly vaccinated. Of those who were at least partly vaccinated, 4·8 million (92·4%) were fully vaccinated, corresponding to 73·8% of Israelis aged 16 years or older being fully vaccinated by the end of the follow-up period. Vaccine coverage was higher and occurred earlier and more rapidly in older age groups (figure 1). For example, among people aged 75 years and older, more than 98·5% (445 707 of 452 596) were at least partly vaccinated and more than 94·8% (429 235 of 452 596) were fully vaccinated by the end of the analysis period.

During the analysis period, there were 269 459 cases of SARS-CoV-2 infection, 13 338 hospitalisations (of which 8429 [63·2%] were severe or critical), and 2859 deaths among people aged 16 years or older. Median daily rate differences between people who were at least partly vaccinated and unvaccinated individuals were 71·8 per 100 000 (IQR 34·3–91·2) for SARS-CoV-2 infections, 3·0 per 100 000 (1·3–4·5) for COVID-19-related hospitalisations, 1·5 per 100 000 (0·5–2·7) for severe or critical COVID-19-related hospitalisations, and

	Total study period (Jan 3*–April 10, 2021†)	Monthly analysis			
		Jan 3–31, 2021	Feb 1–28, 2021	March 1–31, 2021	April 1–10, 2021†
SARS-CoV-2 infections					
Age 16–24 years	75·5 (29·0 to 110·6)	85·7 (52·7 to 119·3)	103·8 (77·9 to 115·5)	35·5 (18·0 to 83·2)	8·4 (8·2 to 11·3)
Age 25–34 years	69·3 (31·6 to 89·2)	72·3 (47·9 to 80·4)	96·0 (74·8 to 108·3)	48·6 (20·9 to 82·4)	16·5 (10·8 to 18·8)
Age 35–44 years	62·7 (28·2 to 78·8)	61·8 (32·3 to 71·3)	82·6 (69·9 to 98·8)	45·3 (30·5 to 79·1)	12·2 (7·1 to 17·5)
Age 45–54 years	58·8 (30·6 to 84·3)	52·4 (32·0 to 64·2)	86·0 (73·2 to 96·5)	52·2 (30·6 to 84·5)	13·3 (9·4 to 17·7)
Age 55–64 years	58·1 (28·7 to 79·2)	58·3 (49·1 to 70·9)	83·5 (66·7 to 91·5)	49·3 (22·3 to 74·4)	10·2 (5·6 to 15·0)
Age 65–74 years	45·2 (24·9 to 61·7)	51·5 (42·0 to 63·2)	61·4 (48·2 to 72·0)	31·4 (19·1 to 45·8)	12·2 (10·3 to 20·6)
Age 75–84 years	66·2 (42·2 to 83·8)	62·8 (51·0 to 70·2)	86·7 (61·7 to 97·7)	65·6 (38·8 to 78·5)	25·4 (14·7 to 35·7)
Age ≥85 years	80·7 (54·7 to 113·0)	94·0 (75·5 to 118·3)	82·9 (64·0 to 140·7)	79·5 (44·8 to 101·9)	18·5 (17·7 to 34·6)
Age ≥16 years	71·8 (34·3 to 91·2)	74·2 (56·3 to 85·1)	96·7 (73·4 to 108·2)	44·1 (24·6 to 81·1)	13·1 (10·4 to 15·9)
COVID-19-related hospitalisations					
Age 16–24 years	0·9 (0·6 to 1·3)	0·8 (0·5 to 0·8)	1·2 (0·9 to 1·5)	1·2 (0·7 to 1·5)	0·4 (0·0 to 0·9)
Age 25–34 years	2·1 (1·4 to 2·8)	1·8 (1·2 to 2·1)	2·6 (2·0 to 3·8)	2·4 (1·6 to 3·1)	1·0 (0·5 to 1·5)
Age 35–44 years	2·3 (1·4 to 3·9)	2·0 (1·5 to 2·5)	3·7 (2·4 to 4·9)	3·7 (1·1 to 4·6)	0·7 (0·0 to 1·3)
Age 45–54 years	4·5 (2·9 to 6·8)	3·4 (2·4 to 4·1)	6·6 (5·6 to 7·7)	5·8 (3·8 to 8·5)	1·2 (1·1 to 2·4)
Age 55–64 years	7·0 (4·1 to 10·0)	5·9 (4·1 to 7·6)	10·6 (8·3 to 12·0)	6·9 (4·1 to 10·5)	0·7 (0·0 to 1·5)
Age 65–74 years	10·3 (6·5 to 14·6)	11·0 (9·5 to 14·1)	13·7 (9·5 to 16·3)	7·9 (5·0 to 13·1)	4·0 (2·1 to 4·1)
Age 75–84 years	27·8 (18·4 to 36·3)	22·6 (18·3 to 27·8)	32·4 (27·4 to 42·4)	32·8 (20·1 to 38·9)	15·5 (14·1 to 21·8)
Age ≥85 years	45·7 (27·1 to 63·8)	46·9 (32·4 to 57·8)	48·0 (39·3 to 69·8)	46·3 (28·9 to 71·7)	0·0 (0·0 to 0·0)
Age ≥16 years	3·0 (1·3 to 4·5)	1·1 (0·4 to 1·5)	4·3 (3·4 to 5·3)	3·8 (2·9 to 5·4)	1·3 (1·1 to 1·7)
Severe or critical COVID-19-related hospitalisations					
Age 16–24 years	0·1 (0·0 to 0·3)	0·1 (0·0 to 0·1)	0·2 (0·1 to 0·4)	0·0 (0·0 to 0·4)	0·0 (0·0 to 0·0)
Age 25–34 years	0·4 (0·1 to 0·9)	0·3 (0·1 to 0·4)	0·7 (0·6 to 1·2)	0·6 (0·0 to 1·2)	0·0 (0·0 to 0·0)
Age 35–44 years	0·9 (0·5 to 1·9)	0·7 (0·5 to 1·0)	1·5 (1·0 to 2·2)	1·2 (0·5 to 2·6)	0·0 (0·0 to 0·0)
Age 45–54 years	2·9 (1·6 to 4·5)	2·0 (1·6 to 2·4)	4·2 (3·3 to 5·0)	3·7 (1·9 to 5·7)	0·6 (0·0 to 1·2)
Age 55–64 years	4·3 (2·8 to 7·3)	3·9 (2·3 to 5·7)	7·3 (5·9 to 8·8)	4·1 (2·8 to 7·8)	0·0 (0·0 to 0·0)
Age 65–74 years	7·6 (4·0 to 11·2)	7·9 (6·4 to 11·0)	10·5 (6·5 to 13·6)	6·5 (2·0 to 11·2)	1·1 (–0·2 to 2·2)
Age 75–84 years	22·9 (13·9 to 29·5)	18·0 (12·9 to 23·4)	27·1 (20·5 to 30·5)	25·8 (13·9 to 33·4)	7·7 (0·0 to 14·6)
Age ≥85 years	33·4 (19·8 to 54·8)	35·8 (25·0 to 56·5)	44·0 (27·9 to 53·6)	31·5 (22·9 to 62·1)	0·0 (0·0 to 0·0)
Age ≥16 years	1·5 (0·5 to 2·7)	0·4 (–0·3 to 0·6)	2·4 (1·8 to 3·2)	2·5 (1·5 to 3·4)	0·4 (0·2 to 0·6)
COVID-19-related deaths					
Age 16–24 years	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)
Age 25–34 years	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·1)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)
Age 35–44 years	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·1)	0·0 (0·0 to 0·2)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)
Age 45–54 years	0·0 (0·0 to 0·4)	0·2 (0·1 to 0·3)	0·1 (0·0 to 0·6)	0·0 (0·0 to 0·8)	0·0 (0·0 to 0·0)
Age 55–64 years	0·5 (0·0 to 1·2)	0·7 (0·2 to 1·2)	0·7 (0·4 to 1·8)	0·0 (0·0 to 1·4)	0·0 (0·0 to 0·0)
Age 65–74 years	2·2 (0·7 to 3·5)	2·5 (1·5 to 3·7)	2·6 (1·2 to 3·9)	2·0 (0·0 to 3·6)	0·0 (0·0 to 0·0)
Age 75–84 years	7·8 (3·5 to 12·6)	7·7 (6·6 to 12·3)	10·1 (6·6 to 15·5)	6·5 (0·0 to 13·1)	0·0 (0·0 to 0·0)
Age ≥85 years	18·1 (7·8 to 29·5)	22·6 (15·8 to 29·5)	23·4 (16·7 to 35·3)	15·2 (0·0 to 38·9)	0·0 (0·0 to 0·0)
Age ≥16 years	0·3 (0·0 to 0·6)	–0·2 (–0·5 to 0·0)	0·4 (0·3 to 0·6)	0·6 (0·3 to 0·7)	0·0 (0·0 to 0·1)

Data are median daily rate difference (IQR) per 100 000 population. *Jan 3, 2021, corresponds to the first day on which people could have been at least partly vaccinated. †April 10, 2021, was the last day of the analysis period. ‡At least partly vaccinated individuals were defined as individuals who received at least one dose of BNT162b2 with at least 14 days of follow-up since the first dose.

Table 1: **Daily rate differences in SARS-CoV-2 outcomes between unvaccinated and at least partly vaccinated‡ individuals by age group, by month and total study period**

0·3 per 100 000 (0·0–0·6) for COVID-19-related deaths (table 1). Time and age stratified results revealed that rate differences varied considerably over time and were generally highest in January and February, 2021, (when SARS-CoV-2 activity was at its peak) and that the largest rate differences in hospitalisations and deaths between unvaccinated people and at least partly vaccinated and fully vaccinated people were observed among people aged 65 years and older (tables 1, 2).

We estimated that 158 665 (95% CI 144 640–172 690) SARS-CoV-2 infections, 24 597 (18 942–30 252) hospitalisations, 17 432 (12 770–22 094) severe or critical

	Total study period (Jan 3*–April 10, 2021†)	Monthly analysis			
		Jan 3–31, 2021	Feb 1–28, 2021	March 1–31, 2021	April 1–10, 2021†
SARS-CoV-2 infections					
Age 16–24 years	91·9 (33·2–135·8)	137·2 (95·2–145·4)	114·6 (89·2–134·4)	38·8 (18·4–88·8)	8·5 (8·3–11·5)
Age 25–34 years	83·1 (39·2–107·5)	99·1 (73·2–108·6)	106·4 (80·6–118·1)	53·2 (22·3–89·6)	16·6 (11·0–19·0)
Age 35–44 years	79·3 (37·6–96·8)	88·4 (71·5–97·7)	91·7 (77·0–107·7)	48·3 (31·0–87·6)	12·6 (7·3–17·4)
Age 45–54 years	83·8 (40·2–100·6)	91·4 (71·5–104·8)	99·6 (81·9–108·1)	54·3 (30·7–88·6)	13·5 (9·4–17·8)
Age 55–64 years	73·7 (34·5–95·2)	92·6 (71·2–107·7)	87·9 (70·2–101·7)	50·4 (23·1–77·9)	10·3 (5·6–15·5)
Age 65–74 years	51·7 (28·4–77·1)	76·0 (59·8–88·8)	64·3 (49·5–79·1)	32·7 (19·7–47·2)	12·3 (10·5–20·8)
Age 75–84 years	73·8 (48·2–93·9)	75·9 (68·1–93·2)	90·9 (63·5–99·6)	67·3 (38·7–82·3)	25·4 (14·7–36·0)
Age ≥85 years	88·8 (61·3–125·8)	116·3 (91·5–156·5)	83·6 (65·4–144·7)	80·1 (46·6–102·5)	18·4 (17·7–34·5)
Age ≥16 years	80·0 (37·2–110·1)	105·6 (79·4–112·1)	103·6 (78·8–118·8)	47·1 (24·9–86·2)	13·2 (10·5–16·1)
COVID-19-related hospitalisations					
Age 16–24 years	1·0 (0·7–1·3)	0·8 (0·7–1·0)	1·2 (1·0–1·6)	1·2 (0·7–1·7)	0·4 (0·0–0·9)
Age 25–34 years	2·1 (1·5–3·0)	1·8 (1·4–2·1)	3·0 (2·1–3·8)	2·4 (1·7–3·5)	1·0 (0·5–1·5)
Age 35–44 years	2·5 (1·5–4·0)	2·2 (1·9–2·9)	3·6 (2·5–4·8)	3·6 (1·2–4·8)	0·7 (0·0–1·3)
Age 45–54 years	4·7 (3·1–7·1)	3·6 (3·1–4·6)	6·7 (5·7–7·6)	6·0 (3·8–9·0)	1·2 (1·2–2·4)
Age 55–64 years	7·4 (5·2–10·6)	7·3 (6·3–8·7)	10·7 (8·8–12·1)	7·2 (4·1–10·5)	0·8 (0·0–1·6)
Age 65–74 years	11·8 (6·8–15·4)	13·3 (10·2–15·3)	13·9 (9·9–17·2)	8·3 (5·1–13·3)	4·1 (2·1–4·2)
Age 75–84 years	29·6 (21·4–37·6)	28·7 (23·7–32·8)	33·3 (27·7–42·9)	32·7 (20·4–38·9)	15·5 (14·1–21·8)
Age ≥85 years	49·3 (29·6–69·3)	56·6 (44·7–70·8)	51·8 (40·0–71·4)	46·2 (28·8–72·6)	0·0 (0·0–0·0)
Age ≥16 years	3·5 (2·7–4·7)	3·2 (2·5–3·8)	4·6 (3·4–5·5)	3·9 (2·9–5·6)	1·3 (1·2–1·7)
Severe or critical COVID-19-related hospitalisations					
Age 16–24 years	0·1 (0·0–0·3)	0·1 (0·0–0·1)	0·2 (0·1–0·4)	0·0 (0·0–0·4)	0·0 (0·0–0·0)
Age 25–34 years	0·4 (0·1–0·9)	0·3 (0·2–0·4)	0·7 (0·6–1·2)	0·6 (0·0–1·2)	0·0 (0·0–0·0)
Age 35–44 years	0·9 (0·6–1·9)	0·8 (0·6–1·2)	1·5 (0·9–2·2)	1·2 (0·6–2·6)	0·0 (0·0–0·0)
Age 45–54 years	3·1 (1·9–4·7)	2·3 (1·9–3·0)	4·2 (3·5–5·0)	3·8 (1·8–5·7)	0·6 (0·0–1·2)
Age 55–64 years	4·7 (3·1–7·6)	4·4 (3·3–5·9)	7·4 (6·0–8·8)	4·1 (2·9–7·8)	0·0 (0·0–0·0)
Age 65–74 years	8·5 (4·4–11·3)	9·0 (7·6–11·1)	10·8 (6·6–13·7)	6·9 (2·0–11·2)	1·1 (0·0–2·2)
Age 75–84 years	24·2 (15·3–30·0)	21·7 (18·0–27·0)	28·5 (21·2–31·4)	26·5 (13·9–34·1)	7·7 (0·0–14·6)
Age ≥85 years	39·0 (23·2–56·7)	43·3 (32·5–61·4)	44·5 (30·1–55·4)	31·5 (22·9–62·1)	0·0 (0·0–0·0)
Age ≥16 years	2·0 (1·4–2·8)	1·7 (1·4–2·1)	2·6 (2·0–3·3)	2·6 (1·5–3·4)	0·4 (0·2–0·6)
COVID-19-related deaths					
Age 16–24 years	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Age 25–34 years	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·1)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Age 35–44 years	0·0 (0·0–0·0)	0·0 (0·0–0·1)	0·0 (0·0–0·2)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Age 45–54 years	0·1 (0·0–0·4)	0·2 (0·1–0·3)	0·2 (0·0–0·6)	0·0 (0·0–0·8)	0·0 (0·0–0·0)
Age 55–64 years	0·6 (0·0–1·4)	0·8 (0·5–1·4)	0·7 (0·5–1·7)	0·0 (0·0–1·4)	0·0 (0·0–0·0)
Age 65–74 years	2·5 (0·9–3·7)	3·0 (2·3–4·5)	2·7 (1·2–4·0)	2·0 (0·0–3·6)	0·0 (0·0–0·0)
Age 75–84 years	9·1 (4·6–13·6)	10·6 (7·4–13·6)	10·5 (6·7–15·7)	6·5 (0·0–13·5)	0·0 (0·0–0·0)
Age ≥85 years	20·2 (9·4–35·4)	29·1 (20·8–37·3)	24·1 (17·3–35·7)	15·2 (0·0–38·9)	0·0 (0·0–0·0)
Age ≥16 years	0·5 (0·3–0·7)	0·6 (0·4–0·7)	0·5 (0·3–0·6)	0·6 (0·3–0·7)	0·0 (0·0–0·1)

Data are median daily rate difference (IQR) per 100 000 population. *Jan 3, 2021, corresponds to the first day on which people could be at least partly vaccinated. †April 10, 2021, was the last day of the analysis period. ‡Fully vaccinated individuals were defined as people who received two doses of BNT162b2 with at least 7 days of follow-up after the second dose.

Table 2: **Daily rate differences in SARS-CoV-2 outcomes between unvaccinated and fully vaccinated‡ individuals by age group, by month and total study period**

hospitalisations, and 5532 (3085–7982) deaths were averted among the at least partly vaccinated population who were aged 16 years or older up to April 10, 2021 (table 3, figure 2). Although adults aged 65 years and older comprised only 1 127 965 (17·3%) of the 6 538 911 population who were aged 16 years or older, who were at least partly vaccinated, they accounted for 16 213 (65·9%) of 24 597 COVID-19-related hospitalisations, 12 611 (72·3%) of 17 432 severe or critical COVID-19-related hospitalisations, and 5035 (91·0%) of 5532 of deaths averted (table 3). We estimated that the fully vaccinated population aged 16 years and older accounted for most of the averted outcomes:

	Population size	SARS-CoV-2 infections averted	COVID-19-related hospitalisations averted	Severe or critical COVID-19-related hospitalisations averted	COVID-19-related deaths averted
Individuals who were at least partly vaccinated*					
Age 16–24 years	1258389	17443 (14839 to 20047)	347 (–6 to 699)	57 (–34 to 149)	5 (–5 to 15)
Age 25–34 years	1231583	20762 (17393 to 24131)	904 (222 to 1586)	229 (–35 to 493)	10 (–11 to 32)
Age 35–44 years	1156876	24255 (19821 to 28690)	1273 (339 to 2207)	579 (8 to 1150)	26 (–28 to 81)
Age 45–54 years	981651	28634 (22440 to 34828)	2544 (785 to 4303)	1595 (283 to 2907)	130 (–117 to 377)
Age 55–64 years	782447	24421 (18141 to 30701)	3316 (1169 to 5463)	2361 (601 to 4120)	326 (–198 to 850)
Age 65–74 years	675369	20332 (13242 to 27422)	4908 (1551 to 8265)	3575 (835 to 6315)	1045 (–282 to 2373)
Age 75–84 years	319285	15025 (7456 to 22594)	6868 (1828 to 11908)	5461 (1085 to 9838)	2070 (–262 to 4402)
Age ≥85 years	133311	7793 (2567 to 13018)	4437 (733 to 8141)	3575 (322 to 6828)	1920 (–242 to 4083)
Age ≥16 years	6538911	158665 (144640 to 172690)	24597 (18942 to 30252)	17432 (12770 to 22094)	5532 (3085 to 7982)
Age ≥65 years	1127965	43150 (31582 to 54717)	16213 (9053 to 23372)	12611 (6423 to 18800)	5035 (1393 to 8678)
Individuals who were fully vaccinated†					
Age 16–24 years	1258389	10282 (8755 to 11810)	220 (–8 to 448)	33 (–19 to 86)	4 (–3 to 11)
Age 25–34 years	1231583	12919 (10842 to 14997)	580 (128 to 1032)	140 (–24 to 305)	6 (–4 to 16)
Age 35–44 years	1156876	17063 (13983 to 20144)	877 (211 to 1543)	398 (–0·4 to 797)	18 (–16 to 52)
Age 45–54 years	981651	21698 (17112 to 26283)	1931 (568 to 3293)	1199 (193 to 2205)	101 (–79 to 281)
Age 55–64 years	782447	19219 (14384 to 24053)	2598 (899 to 4297)	1844 (455 to 3234)	253 (–143 to 649)
Age 65–74 years	675369	16337 (10694 to 21981)	3954 (1221 to 6687)	2865 (653 to 5078)	831 (–213 to 1874)
Age 75–84 years	319285	12390 (6121 to 18659)	5762 (1504 to 10020)	4599 (906 to 8291)	1669 (–227 to 3565)
Age ≥85 years	133311	6092 (1886 to 10297)	3545 (544 to 6546)	2847 (223 to 5472)	1469 (–217 to 3154)
Age ≥16 years	6538911	116000 (106072 to 125928)	19467 (15200 to 23735)	13925 (10408 to 17445)	4351 (2559 to 6140)
Age ≥65 years	1127965	34819 (25428 to 44211)	13261 (7300 to 19222)	10311 (5169 to 15454)	3969 (1022 to 6914)
Individuals who were partly vaccinated‡					
Age 16–24 years	1258389	7161 (6084 to 8237)	127 (2 to 251)	24 (–15 to 63)	1 (–2 to 4)
Age 25–34 years	1231583	7843 (6551 to 9134)	324 (94 to 554)	89 (–11 to 188)	4 (–7 to 16)
Age 35–44 years	1156876	7192 (5838 to 8546)	396 (128 to 664)	181 (8 to 353)	8 (–12 to 29)
Age 45–54 years	981651	6936 (5328 to 8545)	613 (217 to 1010)	396 (90 to 702)	29 (–38 to 96)
Age 55–64 years	782447	5202 (3757 to 6648)	718 (270 to 1166)	517 (146 to 886)	73 (–55 to 201)
Age 65–74 years	675369	3995 (2548 to 5441)	954 (330 to 1578)	710 (182 to 1237)	214 (–69 to 499)
Age 75–84 years	319285	2635 (1335 to 3935)	1106 (324 to 1888)	862 (179 to 1547)	401 (–35 to 837)
Age ≥85 years	133311	1701 (681 to 2721)	892 (189 to 1595)	728 (99 to 1356)	451 (–25 to 929)
Age ≥16 years	6538911	42665 (38568 to 46762)	5130 (3742 to 6517)	3507 (2362 to 4649)	1181 (526 to 1842)
Age ≥65 years	1127965	8331 (6154 to 10506)	2952 (1753 to 4150)	2300 (1254 to 3346)	1066 (371 to 1764)

Data are n or number of cases averted with 95% CI in parentheses. *Individuals who were at least partly vaccinated were those who received at least one dose of BNT162b2 with at least 14 days of follow-up after the first dose. †Fully vaccinated individuals are people who received two doses of BNT162b2 with at least 7 days of follow-up after the second dose. ‡Partly vaccinated individuals are people who received only one dose of BNT162b2 with at least 14 days of follow-up after the first dose or two doses with less than 7 days of follow-up after the second dose.

Table 3: **Estimated SARS-CoV-2 outcomes averted through vaccination programme by number of doses received, Jan 3 to April 10, 2021**

116000 (73·1%) of 158665 SARS-CoV-2 infections, 19467 (79·1%) of 24597 COVID-19-related hospitalisations, 13925 (79·9%) of 17432 severe or critical COVID-19-related hospitalisations, and 4351 (78·7%) of 5532 COVID-19-related deaths (table 3).

Discussion

COVID-19 vaccine uptake in Israel occurred rapidly.[12,15] By the end of the follow-up period (April 10, 2021), Israel had administered more than 2 million doses of Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine per month, resulting in 80% of its population who were aged 16 years or older being at least partly vaccinated and 74% being fully vaccinated. More than 90% of adults aged 65 years or older had received two doses. Since the beginning of the pandemic, Israel has recorded a total of 835811 SARS-CoV-2 infections and 6292 COVID-19-related deaths as of April 10, 2021.[3] Of these, 269459 SARS-CoV-2 infections, 13338 COVID-19-related hospitalisations, 8429 severe or critical COVID-19-related hospitalisations, and 2859 COVID-19-related deaths occurred during the analysis period from Jan 3 to April 10, 2021 among people aged 16 years and older. Up to April 10, 2021, a period of 112 days from the start of the nationwide vaccination campaign, we estimated that vaccination averted 158665 SARS-CoV-2 infections, 24597 COVID-19-related

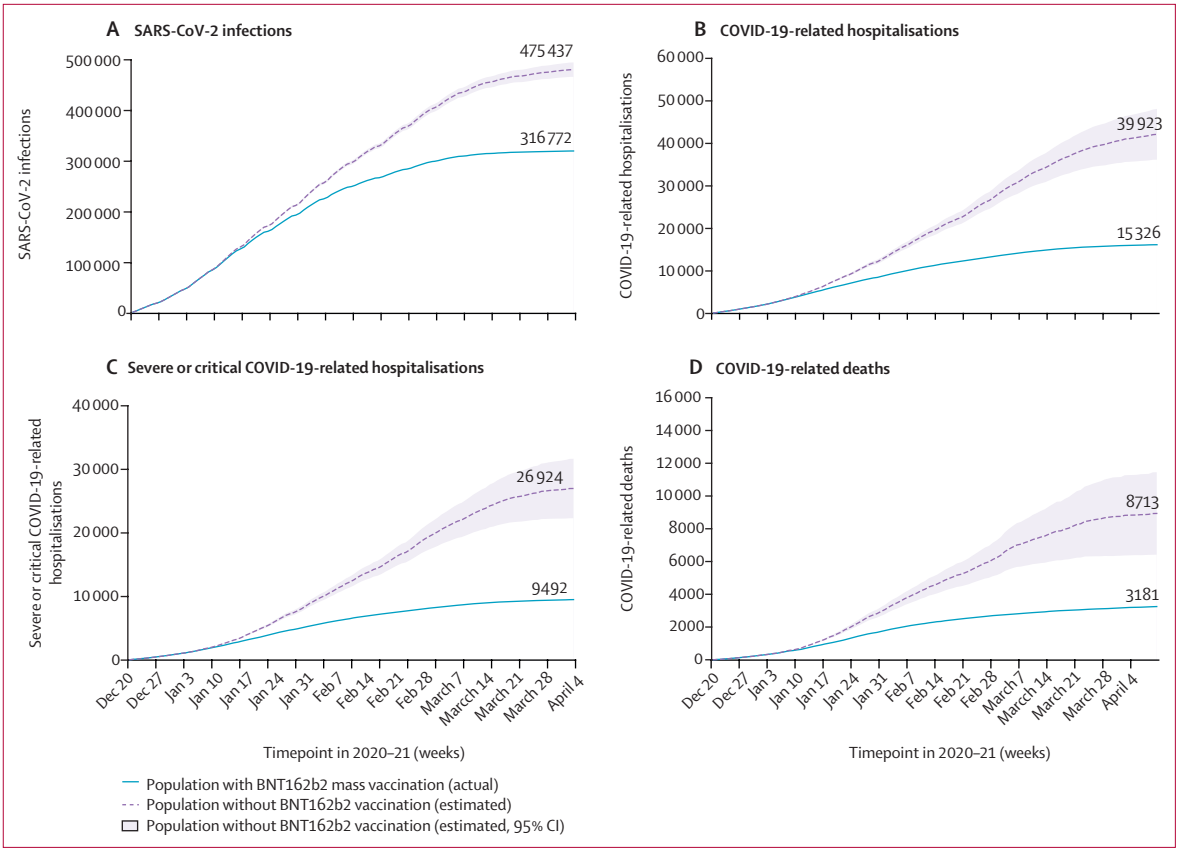

Figure 2: **Cumulative SARS-CoV-2 outcomes over time comparing observed cases with nationwide vaccination and predicted cases without vaccination by outcome, Dec 20, 2020, to April 10, 2021**

(A) SARS-CoV-2 infections. (B) COVID-19-related hospitalisations. (C) Severe and critical COVID-19-related hospitalisations. (D) COVID-19-related deaths. Lines are estimates over time with shaded areas showing 95% CIs.

hospitalisations, 17432 severe or critical COVID-19-related hospitalisations, and 5532 COVID-19-related deaths. Thus, our results suggest that Israel would have had at least three times as many hospitalisations and deaths than actually occurred between the start of the vaccination programme up to April 10, 2021, if not for the rapid implementation of the nationwide vaccination campaign. Based on our estimates, the vaccination campaign averted almost as many deaths as have occurred in Israel during the entire pandemic by the end of the study period. Israel's strategy of prioritising vaccination of older people seemed to have notable effects on directly averting hospitalisations and deaths, and contributed to the relatively high proportion of severe outcomes averted. For example, although adults aged 65 years and older comprised only 17% of the total vaccine-eligible population, this same age group accounted for 66% of hospitalisations, 72% of severe or critical hospitalisations, and 91% of deaths averted by the vaccination campaign. In adults aged 75 years or older, vaccination was especially efficient, averting approximately three hospitalisations and one death per 100 persons in this age group during the first 112 days of the vaccination campaign. Notably, Israel had adequate vaccine supply to provide immunisations to all eligible adults, which made considerations of vaccine schedule and prioritisation less complex than would be the case in a setting with a limited supply of vaccine.

Although we modelled the effect of being at least partly vaccinated, most (92%) of these at least partly vaccinated individuals were actually fully vaccinated. Thus, our results largely reflect the effect of a nationwide vaccination campaign that rapidly resulted in high two-dose coverage. Overall, 73% of SARS-CoV-2 infections and 79% of COVID-19-related hospitalisations and deaths averted were among fully vaccinated people. These data highlight the direct effect of the recommended two-dose schedule, but also elucidate the additional, incremental benefit of protection after only one dose while awaiting completion of the full two-dose schedule. These findings complement our previous vaccine effectiveness assessment in Israel, which showed significant protection 14–21 days after the first dose of BNT162b2, albeit lower than that 6 days or fewer after the second dose.[4]

Our cases-averted model has several limitations. First, rate differences between vaccinated and unvaccinated groups were based on observational data. We stratified our

analysis by age and by date to control for key potential confounders but did not have information describing rates by other factors such as comorbidities, socioeconomic status, and likelihood of seeking SARS-CoV-2 testing, which, as previously described,[4] might vary by vaccination status. Also, unmeasured differences might have existed between vaccinated and unvaccinated people in adherence to non-pharmaceutical interventions (eg, wearing facemasks, handwashing, and physical distancing), which might have confounded our estimates. However, whether people who are at least partly vaccinated are more likely to accept public health recommendations and thus be more adherent to non-pharmaceutical interventions or conversely would be less adherent after being vaccinated (and thereby feel more protected) remains unclear. Real-world vaccine effectiveness results in Israel[4] based on these same national surveillance data were consistent with estimates of efficacy from the randomised controlled trial of BNT162b2.[7] A second limitation is that our analysis does not include potential indirect effects that could have reduced disease burden among the unvaccinated population, including children younger than 16 years who were not eligible for vaccination and were excluded from the analysis. If indirect effects stemming from the vaccination programme were substantial, our results likely underestimate the effect of the nationwide vaccination programme. The potential for indirect effects seems probable on the basis of preliminary evidence suggesting that BNT162b2 has some effectiveness against asymptomatic infections[4] and that the vaccine reduces infectivity[16,17] and provides indirect effects[18,19]—suggesting the vaccine would likely contribute to breaking chains of transmission in the population. Additionally, the long-term effect of high vaccine coverage on keeping the pandemic under control was not accounted for in our model. Future studies should attempt to estimate indirect effects of Israel's COVID-19 vaccination programme, which would be additive to our analysis.

Moreover, we did not assess the effect of the vaccination programme on long-term COVID-19 sequelae nor did we weigh the cases averted against potential adverse effects after immunisation. We did our analysis during a period when the alpha (B.1.1.7) variant of concern accounted for an estimated 95% of strains sequenced in Israel.[4] Future modelling might be needed to assess the effect of any new emerging variants of concern, including the delta variant, which has become the dominant strain in Israel since early June, 2021, or the potential effect of additional booster doses. We also assumed no effect of the vaccine fewer than 14 days after the first dose. This assumption is consistent with the clinical trial experience[7] and assumptions made in our previous analyses of vaccine effectiveness.[3] However, if BNT162b2 provided any protection during this period our cases-averted calculations would be underestimated.

Additionally, because we excluded individuals with previous SARS-CoV-2 infection from our cases-averted calculations, our analysis assumes no effect of vaccination in this group. At the beginning of the study period, 3% of the population aged 16 years or older had a previous SARS-CoV-2 infection, by the end of the study period, 7% had a previous infection. Younger age groups were more likely to be previously infected, with 11% of those aged 16–24 years being previously infected at the end of the study period compared with 4% of those aged 65 years and older. This assumption is probably conservative because previous studies have shown that vaccination can boost immune responses in those who were previously infected.[20] Furthermore, the randomised controlled trial of BNT162b2 showed similar efficacy when individuals who had been previously infected were included,[7] and if vaccination confers better, broader, or longer effectiveness than does natural infection,[21] the effect of the vaccination programme could be even larger than we estimated here.

Because of differences between countries in how vaccines are rolled out, population-level vaccine coverage, and pandemic activity at the time of vaccination, caution should be used when extrapolating our findings to other populations and health-care delivery systems. Another limitation is that a national lockdown occurred at approximately the same time that the vaccination programme began, making it difficult to determine the effects of the vaccination programme from those of the lockdown restrictions. However, we compared daily incidence rates in vaccinated and unvaccinated individuals to account for day-to-day effects of the lockdown and changes in SARS-CoV-2 activity. Moreover, previous assessments of Israel's nationwide surveillance data have suggested that vaccine introduction affected the pandemic independently of the lockdown.[4,16] Additionally, in some instances, 95% CIs were wide, especially for deaths, given variability in day-to-day COVID-19-related mortality rate differences and low numbers of deaths following the roll-out of the vaccination programme.

Finally, although we estimated the public-health effect of the vaccination programme in terms of the number of SARS-CoV-2 infections and COVID-19-related hospitalisations, and deaths averted, future analyses should outline the economic benefit of the vaccination programme, including both the direct medical costs of our estimated averted COVID-19 outcomes, and broader macroeconomic benefits of being able to reopen society, schools, the workplace, and the broader economy.

Without vaccination, Israel would have likely experienced approximately three times the number of hospitalisations and deaths compared with what actually occurred during its largest wave of SARS-CoV-2, which would have likely overwhelmed the health-care system. Indirect effects and long-term benefits of the programme, which could be substantial, were not included in these estimates and warrant future research.

Contributors

All authors contributed to study design, drafting the protocol, and revising the manuscript for important intellectual content, were responsible for the decision to submit for publication, and approved the final submitted

version of the manuscript. All authors had full access to the deidentified and aggregated data in the study. JMM, DLS, and EJH conceived the study. JMM, FK, and EJH did the analysis and edited the final manuscript. JMM, EJH, ML, and FK wrote the first draft of the protocol. EJH, JMM, and FK accessed and verified the data underlying the study and take responsibility for the data.

Declaration of interests

JMM, FJA, FK, GM, KP, JS, DLS, and LJ hold stock and stock options in Pfizer. ML has provided advice on COVID-19 free of charge to Janssen, AstraZeneca, Pfizer, COVAXX (United Biomedical), and to the non-profit organisation One Day Sooner; has received consulting income or honoraria from Merck, Bristol Meyers Squibb, Sanofi, and Morris-Singer Fund; and had received institutional research support from Pfizer. All other authors declare no competing interests.

Data sharing

No individual-level or sensitive data were used in this analysis. Requests for data should be made to the Ministry of Health of Israel. Aggregated surveillance data are freely available online at https://data.gov.il/dataset/covid-19.

For **aggregated surveillance data** see https://data.gov.il/dataset/covid-19

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